International Immunology, Vol. 34, No. 9, pp. 455–466
https://doi.org/10.1093/intimm/dxac030
Advance Access publication 6 July 2022

Published *by Oxford University Press on behalf of The Japanese Society for Immunology 2022.*

Liver cirrhosis and immune dysfunction

Elda Hasa[1,*], Phillipp Hartmann[1,2,3,*] and **Bernd Schnabl[1,4]**

[1]Department of Medicine, University of California San Diego, La Jolla, CA 92093, USA
[2]Department of Pediatrics, University of California San Diego, La Jolla, CA 92093, USA
[3]Division of Gastroenterology, Hepatology and Nutrition, Rady Children's Hospital San Diego, San Diego, CA 92123, USA
[4]Department of Medicine, VA San Diego Healthcare System, San Diego, CA 92161, USA
[*]These authors contributed equally to this article.

Correspondence to: B. Schnabl; E-mail: beschnabl@ucsd.edu

Received 1 May 2022, *editorial decision* 27 June 2022; *accepted* 27 June 2022

REVIEW

Cirrhosis is end-stage liver disease resulting from various etiologies and is a common cause of death worldwide. The progression from compensated to decompensated cirrhosis to acute-on-chronic liver failure (ACLF) is due to multiple factors, including continuation of alcohol use or continued exposure to other toxins, an imbalance of the gut microbiota (dysbiosis), increased gut permeability and a disrupted immune response. This disrupted immune response is also named cirrhosis-associated immune dysfunction, which is characterized by worsening systemic inflammation with concomitant immune paralysis, as liver disease deteriorates. This review highlights central immunologic events during the exacerbation of cirrhosis and characterizes the different immune cell populations involved therein.

Keywords: acute-on-chronic liver failure (ACLF), cirrhosis-associated immune dysfunction (CAID), compensated and decompensated cirrhosis, immune paralysis, inflammation

Introduction

Cirrhosis is currently the eleventh most common cause of death globally, accounting for 2 million deaths per year with an estimated 3.5% of global mortality (1–3). It is the seventh most common cause of disability-associated life-years, or life-years lost due to premature mortality and reduced health (4), in people aged 50–74 years, the twelfth top etiology in the 25–49-year age range, and the sixteenth top cause across all ages (5, 6). Alcohol-associated liver disease (7), chronic viral hepatitis (8) and metabolic-associated fatty liver disease/nonalcoholic fatty liver disease (MAFLD/NAFLD) (9) are the most common causes of cirrhosis worldwide.

Cirrhosis is a progressive and dynamic chronic liver disease; it is the end-stage manifestation of hepatic fibrosis in the setting of chronic liver inflammation, characterized by the formation of regenerative hepatic nodules, separated by fibrotic septa and associated with major distortion in vascular architecture (3, 10). Studies have demonstrated that cirrhosis is no longer considered an irreversible progressive disease, if the cause of the disease is removed (11–13). Cirrhosis is associated with multiple gastrointestinal abnormalities, including impaired bile flow, intestinal dysmotility, altered gastric pH and intestinal innate immune response, and gut microbiome dysbiosis (14–16). Intestinal dysbiosis is defined as a microbial imbalance with its associated deleterious effects on the colonized host (14, 17). However, it is also considered a systemic disease, as it affects most organ systems of the body, including the immune system (18).

In this review, we will describe immunopathologic mechanisms associated with cirrhosis, decompensation of cirrhosis and acute-on-chronic liver failure (ACLF).

Liver decompensation and ACLF

Cirrhosis oftentimes starts with an asymptomatic stage, known as compensated cirrhosis, which can last for multiple years, before it progresses to advanced, decompensated cirrhosis (19). It is estimated that 5–7% of patients with compensated cirrhosis progress to decompensated cirrhosis per year (20). Decompensated cirrhosis is defined as an acute deterioration in liver function in a patient with cirrhosis, including the new onset of portal hypertension, ascites (that is, the accumulation of large amounts of fluid within the peritoneal cavity), variceal hemorrhage, hepatic encephalopathy and jaundice among other symptoms (21, 22).

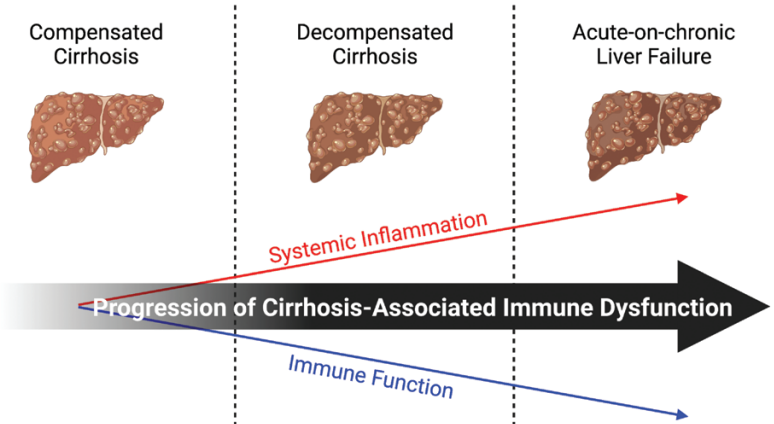
An acute precipitating event (hepatic or extrahepatic) can occur at any time from compensated to decompensated stages, such as bacterial infection or active alcoholism that may challenge liver homeostasis, producing a life-threatening syndrome called ACLF (23, 24). ACLF is a severe syndrome of acutely decompensated cirrhosis and is characterized by

the presence of organ system dysfunction and failures in one or more major organ systems including the liver, kidneys, brain, coagulation, circulation and respiratory system (23, 24). Organ failure is the feature that differentiates ACLF from decompensated cirrhosis without ACLF; the most affected organs are liver and kidney, resulting in high short-term mortality (23, 24). Similar to decompensated cirrhosis, ACLF is characterized by the presence of systemic inflammation, although even more severe, which is associated with higher mortality (25).

Cirrhosis-associated immune dysfunction syndrome

Cirrhosis and ACLF are associated with moderate and severe systemic inflammation, respectively, with increased inflammatory cytokines, oxidative stress, and markers of activated neutrophils and macrophages in the blood and in the liver (19, 23, 26, 27). Translocation of bacterial products from the gut into the bloodstream secondary to intestinal dysbiosis, increased intestinal permeability and impaired gut immunity promotes systemic inflammation (14–16, 26, 28). Inflammatory markers can have predictive implications in this setting; the magnitude of the white blood count predicts the development of ACLF, ACLF progression and related mortality (23, 27, 29); the neutrophil to lymphocyte ratio predicts short-term mortality (30); and procalcitonin (31–34) and C-reactive protein (CRP) (23, 31, 32, 34–36) predict infection and short-term mortality in decompensated cirrhotic patients. Although systemic inflammation occurs in liver cirrhosis, an "immune paralysis" or immune deficiency is often observed, a clinical state that has been called cirrhosis-associated immune dysfunction syndrome (18, 37). The intensity of cirrhosis-associated immune dysfunction correlates with the severity of liver insufficiency, bacterial translocation and organ failure (37).

When cirrhosis progresses from compensated to decompensated stages to ACLF, systemic inflammation and cirrhosis-associated immune dysfunction with immune deficiency worsen (Fig. 1): while inflammatory cytokines, such as tumor necrosis factor (TNF), interleukin 6 (IL6), IL8, macrophage chemotactic protein 1 [MCP1, also known as C–C motif chemokine ligand 2 (CCL2)], macrophage inflammatory protein 1 beta (MIP1B, also known as CCL4), interferon gamma-inducible protein 10 [IP-10, also known as C–X–C motif chemokine ligand 10 (CXCL10)] and granulocyte colony-stimulating factor (GCSF) (25, 38–40), successively increase during that sequence; a few anti-inflammatory cytokines,



Acute-Phase Proteins	CRP	↑	↑↑
Inflammatory Cytokines	TNF, IL-6, IL-8, CCL2, CCL4, CXCL10, GCSF	↑	↑↑
Anti-Inflammatory Cytokines	IL10, IL1RN	↑	↑↑
Neutrophils	Phagocytosis Oxidative Burst	↓ ↑	↓ ↑
Monocytes	Phagocytosis Superoxide Production HLA-DR and TNF	↓ ↓ ↑	↓ ↓ ↓

Fig. 1. Progression of cirrhosis-associated immune dysfunction during deterioration of cirrhosis. Cirrhosis-associated immune dysfunction worsens with more-severe systemic inflammation and immune deficiency, while cirrhosis progresses from compensated to decompensated stages to ACLF. Worsening of cirrhosis-associated immune dysfunction is expressed by increasing acute-phase proteins, such as CRP; increasing inflammatory cytokines, i.e. TNF, IL6, IL8, MCP1 (CCL2), MIP1B (CCL4), IP-10 (CXCL10) and GCSF; increasing anti-inflammatory cytokines, including IL10 and IL1RN; decreased phagocytosis and increased oxidative burst by neutrophils; decreased phagocytosis and superoxide production by monocytes, and increased monocytic HLA-DR expression and *ex vivo* TNF production in decompensated cirrhosis, which are decreased in ACLF. Created with a license from Biorender.com.

including IL10 and the IL1-receptor antagonist (IL1RN), also increase (25, 39). Immune deficiency is characterized by decreased neutrophilic phagocytosis and increased respiratory burst in decompensated cirrhosis (41–44) and ACLF (45, 46). Phagocytosis (47) and superoxide production by monocytes (48) are decreased in cirrhosis and deteriorate with severity of cirrhosis. Monocytic human leukocyte antigen-DR (HLA-DR) expression and *ex vivo* TNF production are increased in decompensated cirrhosis (49), whereas both are reduced in ACLF (39, 50, 51).

Infections in cirrhosis including spontaneous bacterial peritonitis

Ascites (derived from *askos*, Greek, meaning "bag" or "sack" (52)), is the most common complication of decompensated cirrhosis with more than 50% of patients developing ascites within 10 years of diagnosis (53, 54). It is associated with a poor 5-year survival of 56.5% (55), which is oftentimes due to an infectious etiology, including spontaneous bacterial peritonitis (55), urinary tract infection, pneumonia (56) or fungal infections (57). Cirrhosis-associated immune dysfunction allows life-threatening infections in this clinical context (37). Spontaneous bacterial peritonitis is the most frequent infection in cirrhotic patients with ascites, traditionally diagnosed by diagnostic paracentesis, identifying an ascitic fluid polymorphonuclear cell count ≥ 250 cells per mm^3 (58, 59), and it is associated with a high 1-year mortality rate of over 80% (59). Interestingly, a polymorphonuclear cell count ≥ 125 cells per mm^3 has been found to have a similar 1-year mortality rate with only 25% of the patients surviving (59). Urinary tract infection is the second most common bacterial infection in cirrhosis after spontaneous bacterial peritonitis (56).

An important event in disease progression in cirrhosis is bacterial translocation, which is defined as the migration of viable bacteria or bacterial products from the intestinal lumen to mesenteric lymph nodes or other extraintestinal organs and sites (60, 61). Factors leading to increased bacterial translocation in cirrhotic patients are intestinal bacterial overgrowth, deficiencies in host immune defenses and increased permeability or damage to the intestinal mucosal barrier (61, 62). Additionally, gene polymorphisms in toll-like receptor 2 (TLR2) and nucleotide oligomerization domain 2 (NOD2) have been linked to bacterial translocation and spontaneous bacterial peritonitis (63–65). Further, the microbiome is profoundly distorted in cirrhosis, which is partly secondary to altered motility of the small bowel (66, 67), changed bile acid metabolism (68, 69), reduced bile flow (14, 70) and widespread proton-pump inhibitor usage (14, 71). Patients with liver disease and in particular cirrhosis also experience fungal dysbiosis with increased fungal products in the systemic circulation (72–75). Use of antibiotics and proton-pump inhibitors is a risk factor for fungal dysbiosis in cirrhosis (76). One of the fungal infections in patients with cirrhosis is spontaneous fungal peritonitis (57), which has a 1-month mortality rate in the range 50–73% (77–79). Microbiome-based interventions to improve dysbiosis and disease burden have been recently reviewed in various liver diseases including cirrhosis (80).

Intestinal and hepatic firewalls

The mesenteric lymph nodes contribute to the intestinal firewall as the first line of defense against invading gut microbes; the liver is a vascular firewall and second firewall that captures microbes translocated from the gut into portal circulation (81). In particular, resident liver macrophages, or Kupffer cells, phagocytose and clear translocated microbes in the liver independently from the spleen (81).

In cirrhosis, intestinal permeability and bacterial translocation are increased (82–84), which results in activation of intestinal immune cells and intestinal inflammation (85–87). Intestinal inflammation can further contribute to intestinal permeability and bacterial translocation (88). With increasing bacterial translocation, the first intestinal firewall becomes overwhelmed and is not able to clear microbes. Bacteria and bacterial products such as lipopolysaccharides (LPS) or other microbial products enter the portal vein blood, and the second firewall in the liver becomes more important for clearance (81). In health, low amounts of LPS reach the liver enabling a tolerogenic environment (89). In (liver) disease, Kupffer cells effectively kill translocated bacteria and bacterial products, assisted by LPS-binding protein and TLR4 (the cellular LPS receptor) enhancing the uptake by Kupffer cells (90–92). However, if bacterial translocation worsens and persists, overwhelming both firewalls, liver inflammation induced by Kupffer cells and other immune cells develops, associated with hepatocyte death, and induction and progression of hepatic fibrosis by hepatic stellate cells (14, 15).

The features and mechanisms of various hepatic and systemic immune deficiencies commonly seen in cirrhosis and ACLF are summarized below (Table 1).

Deficient hepatic immunity

Reduction of complement receptor of immunoglobulin on Kupffer cells

Complement receptor of immunoglobulin [CRIg, also known as V-set immunoglobulin-domain-containing 4 (VSIG4)] is expressed on Kupffer cells and binds directly to Gram-positive bacteria or binds to complement C3b to mediate phagocytosis (93–96). Patients with alcohol-associated liver disease or hepatitis have decreased expression of CRIg in their livers, and CRIg-deficient mice were found to have more-severe ethanol-induced liver disease compared with wild-type littermate mice (93). Further, CRIg-deficient mice were less efficient at clearing the Gram-positive bacterium *Enterococcus faecalis* in the liver after it translocated from the gut (93). Administration of the soluble immunoglobulin-like domain of CRIg (CRIg-Ig) ameliorates ethanol-induced liver disease in mice (93). In another study, CRIg/VSIG4 has been studied in spontaneous bacterial peritonitis: Peritoneal macrophage activation by infection with live bacteria *in vitro* resulted in a loss of surface VSIG4 and the release of soluble VSIG4 (97). A higher concentration of ascitic soluble VSIG4 has been found to indicate a higher 90-day mortality in spontaneous bacterial peritonitis (97). These findings indicate the important role of CRIg/VSIG4 in clearing translocated bacteria from the liver and preventing liver disease or spontaneous bacterial peritonitis, a mechanism that is deficient in patients

Table 1. Mechanisms of immune deficiency in cirrhosis

Location		Mechanism		Results	Contributing Factors
Hepatic	Defective anti-infective protein production	↓ Pattern recognition receptors ↓ Complements and complement receptors	→	↓ Recognition ↓ Opsonization ↓ Clearing of pathogens and pathobionts	Genetics (such as polymorphisms)
		Immune cells			
Systemic	Defective systemic immune cells	Neutrophils ↓ Cell count ↓ Phagocytosis ↑ Oxidative burst ↓ Chemotaxis	→	Ineffective killing of pathogens and pathobionts	Genetics, environmental factors (e.g. alcohol use)
		Monocytes ↑ Cell count ↓ Phagocytosis ↓ Superoxide production ↓ Chemotaxis	→	Ineffective killing of pathogens and pathobionts	Genetics, environmental factors (e.g. viruses, alcohol use)
		Natural killer cells ↓ Cell count ↓ Lysis	→	Ineffective killing of pathogens and pathobionts	Genetics, environmental factors (e.g. diet, smoking, alcohol use)
		B cells ↓ Cell count ↓ Immunoglobulin production	→	↓ Opsonization ↓ Killing ↓ Vaccine responsiveness	Genetics, environmental factors (e.g. alcohol use)
		T cells ↓ Cell count ↑ Apoptosis ↓ Proliferation	→	Ineffective killing of pathogens and pathobionts	Genetics, environmental factors (e.g. alcohol use)
Gut-associated lymphoid tissue	Defective intestinal immune cells	T cells, monocytes, dendritic cells ↑ Continuous activity ↑ Cytokine production ↑ Phagocytosis	→	↑ Gut inflammation ↑ Gut permeability ↑ Systemic inflammation	Genetics

with decompensated cirrhosis and alcohol-associated hepatitis. Furthermore, the overall reticuloendothelial system phagocytic activity, estimated by the plasma elimination rate constant of ^{99m}technetium-sulfur colloid, is a significant prognostic factor for patients with decompensated cirrhosis, with a decreased phagocytic activity being associated with more bacterial infections and worse survival (98).

Diminished production of other anti-infective proteins

Cirrhosis dampens the synthesis of other proteins involved in immunity, including the serum and ascitic levels of the complement components C3 and C4 and the total hemolytic component (CH_{100}), resulting in decreased opsonic activity and higher likelihood of spontaneous bacterial peritonitis and mortality (99–105). In contrast, alcoholic hepatitis patients have upregulated hepatic C1q and C5 mRNA expression (106). Polymorphisms of pattern-recognition receptors can play a major role as well in liver disease: the risk of severe infections and mortality after liver transplantation depend on polymorphisms and the resulting level of mannose-binding lectin, a recognition molecule of the lectin pathway of complement and a key component of innate immunity (107–111).

Deficient systemic immunity

Deficiency in neutrophils

Portal hypertension-induced splenic sequestration of blood cells, including immune cells (112), results in a numeric deficiency of neutrophils in cirrhosis. Neutrophils are functionally deficient with reduced phagocytosis and a defective oxidative burst with altered superoxide anion production and myeloperoxidase activity (41–46). Decreased chemotaxis reduces neutrophil function as well (42). Alcohol itself reduces neutrophil function further (113). Moreover, neutrophilic phagocytosis depends on genetics, as shown in chronic granulomatous disease (CGD), which can be due to various gene mutations, classically X-linked but also autosomal (114). Other conditions secondary to gene mutations can also display decreased neutrophil chemotaxis and superoxide anion production [e.g. Rac Family Small GTPase 2 (Rac2) mutation] (115).

Deficiency in monocytes

Monocytes are more numerous in cirrhosis because of an expansion of inflammatory $CD14^+CD16^+$ monocytes (116, 117). However, phagocytosis, superoxide production and chemotaxis are also defective in monocytes in cirrhosis, similar to neutrophils (47, 48, 104, 118–120). The function of monocyte Fc-gamma receptors is impaired in patients with cirrhosis, which likely contributes to a higher risk of bacterial infections in these patients (47). Contributing to this deficiency, ethanol decreases Fc-gamma receptor-dependent rosette formation by monocytes and their phagocytic capacity (121). HLA-DR expression and *ex vivo* TNF synthesis by monocytes are heightened in decompensated cirrhosis (49) but decreased in ACLF (39, 50, 51). Similarly, patients with immune-active chronic hepatitis B exhibit an expansion of inflammatory $CD14^+CD16^+$ monocytes that express higher levels of HLA-DR (122), which could enhance the findings above in the appropriate setting. The inflammatory cytokine CCL2 (MCP1) is a potent chemoattractant for monocytes and its serum level increases with severity of cirrhosis (25, 40). Of note, the AA genotype of CCL2 is a risk factor for development of spontaneous bacterial peritonitis (123).

Deficiency in natural killer cells

Natural killer cells show defective response to cytokines and decreased cytolytic activity in cirrhosis (124–126). Acute alcohol ingestion suppresses natural killer cell activity (127) and chronic alcohol use increases their activity, whereas patients with alcohol-related cirrhosis again show reduced natural killer cell activity (125). Another study demonstrated other environmental factors influence natural killer cell activity, including cigarette smoking, intake of green vegetables, meat, dairy products and soybeans (128). Natural killer cells exhibit antifibrotic properties by killing hepatic stellate cells involving various mechanisms, including TNF-related apoptosis-inducing ligand (TRAIL), Fas ligand and the natural killer cell receptors NKG2D and NKp46. This antifibrotic activity is inversely correlated with fibrosis stage (129–131). Mutations related to NKG2D and NKp46 were shown to modulate natural killer cell activity (132, 133).

Deficiency in B lymphocytes

The B cell population is markedly reduced in cirrhosis (134–137). This includes an important subset, $CD27^+$ memory B cells, which also shows impaired inflammatory function and ability to synthesize immunoglobulins, resulting in low vaccine responsiveness and higher susceptibility to bacterial infections (137). Alcohol might contribute to the B cell phenotype as well at least partially, since patients with alcohol use disorder exhibit similar findings with reduced B cell counts (138, 139) with abnormal maturation, diminished antigen-specific antibody responses (140) but overall increased total IgA, IgG, and IgM (139, 141). Various gene mutations can arrest B cell maturation resulting in agammaglobulinemia including mutations in Bruton's tyrosine kinase (Btk) (142), severely affecting the function of B cells.

Deficiency in T lymphocytes

T cell lymphopenia, including $CD4^+$ and $CD8^+$ T cells, is frequently observed in cirrhosis (49, 143–145). Both activated $CD4^+$ and $CD8^+$ T cells exhibit higher expression of apoptosis markers (146). Circulating T cells also show reduced proliferative function (147, 148). Similarly, ethanol decreases cell counts and increases apoptosis of thymocytes (149) and T cells (150, 151). Single nucleotide polymorphisms (SNPs) of multiple genes, including CD28, CD86, and cytotoxic T lymphocyte associated protein 4 (CTLA4) can modulate T cell activation (152).

Deficient gut-associated lymphoid tissue immunity

The gut-associated lymphoid tissue forms the barrier for defense against pathogens from the gut (61). It comprises multi-follicular Peyer's patches, the vermiform appendix

and the numerous isolated lymphoid follicles (153). In cirrhosis, the gut-associated lymphoid tissue is highly active secondary to sustained bacterial translocation from the gut related to increased gut permeability (85). This increased activity is evident from increased numbers of activated T cells, monocytes and dendritic cells in the lamina propria and in mesenteric lymph nodes (85–87). This results in increased cytokine expression and phagocytosis locally (85–87). Interestingly, non-absorbable antibiotics have been shown to reduce this inflammation, which also indicates the role of intestinal dysbiosis in that pathologic process (85–87). Alcohol can also decrease the total number of lymphocytes, B cells, T cells, and macrophages in the intestinal lamina propria and mesenteric lymph nodes (154–156). Intestinal inflammation promotes the worsening systemic inflammation during the progression of cirrhosis (49, 86). Moreover, there is evidence that intestinal inflammation alters intestinal tight-junction protein expression and barrier function in compensated and decompensated cirrhosis (82–84). Gut dysbiosis and bacterial translocation are also facilitated by depressed expression of antimicrobial peptides, including regenerating islet-derived 3 beta (Reg3b) and gamma (Reg3g) (157–159).

Potential targets for cirrhosis-associated immune dysfunction and clinical trials

Treatment of cirrhosis-associated immune dysfunction has to be nuanced, since blunt suppression of systemic inflammation alone might put patients with cirrhosis-associated immune dysfunction at higher risk of bacterial infections, which is a frequent contributor to mortality in patients with compensated and decompensated cirrhosis, and ACLF (160). It is hence important to attempt modulating cirrhosis-associated immune dysfunction in more subtle ways (Fig. 2).

Microbiome and bacterial translocation

The microbiome and bacterial translocation play a central role in the pathogenesis of cirrhosis-associated immune

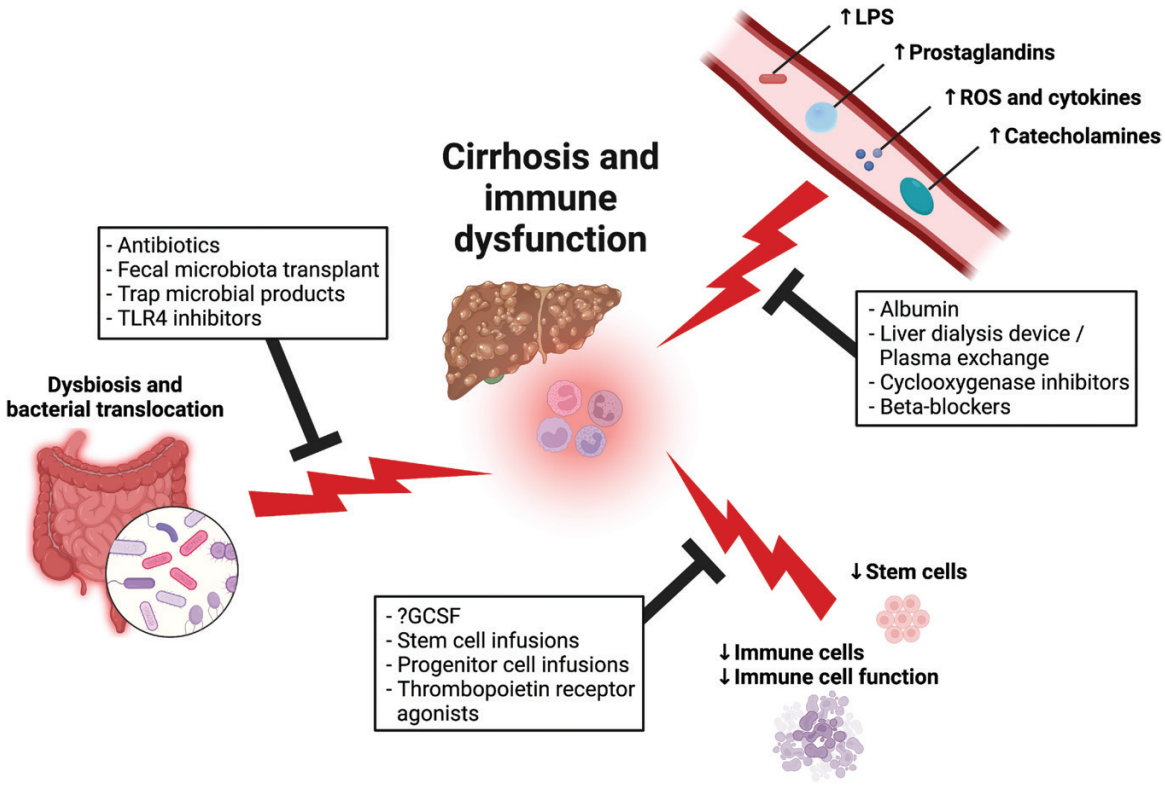


Fig. 2. Targets to ameliorate cirrhosis and cirrhosis-associated immune dysfunction. Dysbiosis and bacterial translocation, aberrant circulating blood factors and immune cell abnormalities contribute to the pathogenesis and deterioration of cirrhosis and cirrhosis-associated immune dysfunction. Dysbiosis, intestinal inflammation and bacterial translocation can be reduced by antibiotics (e.g. norfloxacin) and fecal microbiota transplant. Yaq-001, a novel carbon absorbent that can absorb LPS and inflammatory cytokines, and TAK-242, an inhibitor of the important LPS receptor TLR4, are currently being evaluated in clinical studies for their use in cirrhosis and ACLF. Elevated circulating factors in the blood, including LPS and other microbial products, prostaglandins, reactive oxygen species (ROS), cytokines and catecholamines, worsen systemic inflammation and cirrhosis. Administration of albumin ameliorates inflammation and cirrhosis by binding these mediators. Liver dialysis devices and plasma exchange strategies remove noxious agents. Cyclooxygenase inhibitors reduce prostaglandin levels and beta-blockers attenuate the effects of catecholamines, improving systemic inflammation and the liver phenotype. Hematopoietic and mesenchymal stem cells as well as a variety of immune cells are markedly decreased and the immune cells do not function properly, worsening systemic inflammation. Administration of GCSF has shown promise in some studies, however it did not show a benefit in others. Infusions with stem cells and progenitor cells have shown beneficial immunomodulatory effects and improved outcome in cirrhosis and ACLF. Thrombopoietin receptor agonists are currently being investigated in clinical studies to improve thrombocytopenia in patients with ACLF. Created with a license from Biorender.com.

dysfunction, and intestinal dysbiosis with its associated intestinal inflammation can be ameliorated with non-absorbable antibiotics (85–87). Clinical trials demonstrated the beneficial use of antibiotics in preventing decompensation of cirrhosis. Prophylactic norfloxacin significantly decreases bacterial infections in cirrhotics with ascites (161), 6-months mortality in patients with advanced cirrhosis (162), as well as recurrence of spontaneous bacterial peritonitis in patients with cirrhosis (163). On the other hand, long-term norfloxacin prophylaxis was independently associated with the development of multidrug-resistant bacterial infections in cirrhotics (164), which is an important cause of mortality in patients with cirrhosis and ACLF (165). Other antibiotics are currently being studied in this setting, including co-trimoxazole as primary prophylaxis for spontaneous bacterial peritonitis to improve overall survival in cirrhotics in a phase 3 clinical trial (NCT04395365) and the combination of rifaximin and simvastatin in patients with decompensated cirrhosis to prevent ACLF development and reduce complications and mortality in a phase 3 clinical trial (NCT03780673). Modulation of the intestinal microbiome via fecal microbiota transplantation is beneficial: significantly more patients with severe alcoholic hepatitis were alive at 3 months after receiving a fecal microbiota transplant daily for 7 days compared with patients who received steroids, pentoxifylline or nutrition only (166). The benefit of the fecal microbiota transplant was still present at 3 years compared with standard of care (P = 0.05) with significantly fewer episodes of ascites and infections (167). A similar study is currently ongoing comparing fecal microbiota transplant plus plasma exchange plus tenofovir vs tenofovir only in hepatitis B virus-related ACLF (NCT04431375). Yaq-001 is a novel synthetic carbon that can absorb bacterial products such as LPS and inflammatory cytokines, and is currently being evaluated in a phase 2 clinical trial in cirrhotics with ascites (NCT03202498). TAK-242 is an inhibitor of TLR4, an important cellular LPS receptor on Kupffer cells and other myeloid cells (90), and is currently being assessed in patients with ACLF with regard to its impact on ACLF severity, mortality, and safety (NCT04620148).

Circulating blood factors

Besides LPS, various other blood factors are known to be increased in (advanced) cirrhotics including prostaglandins (168), inflammatory markers, and catecholamines (169), which might exacerbate immune dysfunction. Multiple studies showed that albumin treatment improved mortality in cirrhotic patients with spontaneous bacterial peritonitis (170) and cirrhotic patients with ascites (171), likely due to its capacity to bind LPS and other bacterial products (lipoteichoic acid and peptidoglycan), reactive oxygen species, nitric oxide and other nitrogen reactive species, and prostaglandins (26, 168). Albumin administration is currently being evaluated in a clinical trial for volume resuscitation in cirrhosis with sepsis-induced hypotension (NCT05059795). A liver dialysis device termed DIALIVE removes albumin-toxin complexes, repletes albumin levels, and removes LPS from the circulation, and has been found to reduce mortality secondary to acetaminophen-induced acute liver failure by 67% (172). Its safety and performance in ACLF are currently being investigated in a clinical trial (NCT03065699). A phase 3 trial is enrolling patients with cirrhosis and ACLF to compare plasma exchange with albumin infusion vs standard of care for short-term survival (NCT03702920). Various other liver dialysis/plasma exchange systems are currently studied in clinical trials (NCT04597164, NCT04195282). Cyclooxygenase-derived eicosanoid prostaglandin E2 drives immunosuppression in patients with acute decompensation of cirrhosis, and treatment with cyclooxygenase inhibitors or albumin restored immune competence and survival following infection with group B *Streptococcus* in mouse models of cirrhosis (168). Further, a cyclooxygenase-2 inhibitor was found to reduce liver stiffness in pediatric chronic liver disease patients following Kasai portoenterostomy for biliary atresia (173), but no studies involving adult patients with cirrhosis or ACLF evaluating cyclooxygenase inhibitors have been carried out to date. Blood noradrenaline and adrenaline levels are significantly elevated in cirrhotics compared with controls (169). Moreover, noradrenaline levels are higher in ACLF than in acute decompensation and they are higher in acute decompensation than in stable cirrhosis (27). Its levels correlate with inflammatory markers and are highly predictive of 3-month mortality with an area under the receiver operating characteristic curve (AUROC) of 0.91 (27). Interestingly, a retrospective study involving 349 patients showed that use of nonselective beta-blockers decreases systemic inflammation and mortality in ACLF (174). These findings were confirmed in a recent prospective study that showed beta-blockers significantly improve 28-day mortality with lower incidence of acute kidney failure and spontaneous bacterial peritonitis in ACLF, although there was no difference of these measures at 90 days between treatment and placebo groups (175). A similar study about beta-blockers in patients with cirrhosis and uncomplicated ascites is currently ongoing (NCT05057572).

Blood cells

The bone marrow of patients with more advanced cirrhosis (Model of End-Stage Liver Disease, or MELD scores > 15) is markedly abnormal with significantly decreased $CD34^+$ hematopoietic stem cells and mesenchymal stem cells and increased inflammatory markers such as IL1b and TNF compared with cirrhotics with a MELD score ≤ 15 (176). Administration of GCSF has improved mobilization of $CD34^+$ cells, survival, liver stiffness/MELD scores, and infections/sepsis in clinical trials with patients with decompensated cirrhosis (177) and ACLF (178). However, a recent multicenter trial did not show a benefit of GCSF treatment for 90-day transplant-free survival and 360-day transplant-free and overall survival nor was there a difference regarding infection rate when compared with placebo (179). Stem cell infusions have shown promise in ACLF: umbilical cord-derived mesenchymal stem cell infusions every 4 weeks for three times increased survival at 72 weeks and decreased MELD scores, alanine aminotransferase, and total bilirubin levels at 48 weeks in hepatitis B virus-associated ACLF compared with patients who received saline infusions (180). In a similar study, weekly infusions of allogeneic bone marrow-derived mesenchymal stem cells for 4 weeks resulted in significantly lower mortality, MELD scores, and severe infections in hepatitis B virus-associated ACLF compared with standard of care (181). Human allogeneic liver-derived progenitor cells (HALPC) are derived from the parenchymal

fraction of healthy human liver tissue and have a liver-specific homing capacity after peripheral intravenous infusion (182). They possess immunomodulatory and antifibrotic properties and were found safe in a recent pilot study in acute decompensation of cirrhosis and ACLF (182, 183). They are currently being evaluated in a phase 2b clinical trial in ACLF patients (NCT04229901). To address the thrombocytopenia frequently observed in advanced liver disease, avatrombopag, a thrombopoietin receptor agonist, is currently being investigated in a phase 4 clinical trial in patients with hepatitis B virus-related ACLF receiving double plasma molecular adsorption system and low volume plasma exchange (NCT05382013).

Conclusions

Multiple factors contribute to the progression of liver disease to compensated, decompensated cirrhosis, and ACLF. A hallmark of this progression is cirrhosis-associated immune dysfunction, characterized by worsening systemic inflammation and immune paralysis, which enables life-threatening infections. Future interventions to thwart this progression should be trialed at different levels, including the gut microbiome, the intestinal barrier, as well as intestinal, hepatic and systemic immune cells among others.

Funding

This work was supported in part by National Institutes of Health (NIH) grant K12 HD85036, University of California San Diego Altman Clinical and Translational Research Institute (ACTRI)/NIH grant KL2TR001444, Pinnacle Research Award in Liver Diseases Grant #PNC22-159963 from the American Association for the Study of Liver Diseases Foundation (to P.H.), NIH grants R01 AA24726, R01 AA020703, U01 AA026939, by Award Number BX004594 from the Biomedical Laboratory Research & Development Service of the VA Office of Research and Development, and a Biocodex Microbiota Foundation Grant (to B.S.) and services provided by NIH research center grants P30 DK120515 and P50 AA011999.

Author contributions

E.H. and P.H. were responsible for writing the manuscript, B.S. edited the manuscript.

Conflicts of interest statement: B.S. has been consulting for Ambys Medicines, Ferring Research Institute, Gelesis, HOST Therabiomics, Intercept Pharmaceuticals, Mabwell Therapeutics, Patara Pharmaceuticals and Takeda. B.S.'s institution UC San Diego has received grant support from Artizan Biosciences, Axial Biotherapeutics, BiomX, CymaBay Therapeutics, NGM Biopharmaceuticals, Prodigy Biotech and Synlogic Operating Company. B.S. is founder of Nterica Bio.

References

1 Asrani, S. K., Devarbhavi, H., Eaton, J. and Kamath, P. S. 2019. Burden of liver diseases in the world. *J. Hepatol.* 70:151.
2 Mokdad, A. A., Lopez, A. D., Shahraz, S. *et al.* 2014. Liver cirrhosis mortality in 187 countries between 1980 and 2010: a systematic analysis. *BMC Med.* 12:145.
3 Ginès, P., Krag, A., Abraldes, J. G. *et al.* 2021. Liver cirrhosis. *Lancet* 398:1359.
4 Salomon, J. A., Vos, T., Hogan, D. R. *et al.* 2012. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. *Lancet* 380:2129.
5 GBD 2019 Diseases and Injuries Collaborators 2020. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 396:1204.
6 Ginès, P., Castera, L., Lammert, F. *et al.* 2022. Population screening for liver fibrosis: toward early diagnosis and intervention for chronic liver diseases. *Hepatology* 75:219.
7 Crabb, D. W., Im, G. Y., Szabo, G. *et al.* 2020. Diagnosis and treatment of alcohol-associated liver diseases: 2019 practice guidance from the American Association for the Study of Liver Diseases. *Hepatology* 71:306.
8 Perz, J. F., Armstrong, G. L., Farrington, L. A. *et al.* 2006. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. *J. Hepatol.* 45:529.
9 Eslam, M., Sanyal, A. J. and George, J. 1999. International Consensus Panel. 2020. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. *Gastroenterology* 158:1999.
10 Goossens, N., Nakagawa, S. and Hoshida, Y. 2015. Molecular prognostic prediction in liver cirrhosis. *World J. Gastroenterol.* 21:10262. doi:10.3748/wjg.v21.i36.10262.
11 Bonis, P. A., Friedman, S. L. and Kaplan, M. M. 2001. Is liver fibrosis reversible? *N. Engl. J. Med.* 344:452. doi:10.1056/NEJM200102083440610.
12 Jung, Y. K. and Yim, H. J. 2017. Reversal of liver cirrhosis: current evidence and expectations. *Korean J. Intern. Med.* 32:213.
13 Ramachandran, P., Iredale, J. P. and Fallowfield, J. A. 2015. Resolution of liver fibrosis: basic mechanisms and clinical relevance. *Semin. Liver Dis.* 35:119.
14 Hartmann, P., Chen, W. C. and Schnabl, B. 2012. The intestinal microbiome and the leaky gut as therapeutic targets in alcoholic liver disease. *Front. Physiol.* 3:402.
15 Hartmann, P., Seebauer, C. T. and Schnabl, B. 2015. Alcoholic liver disease: the gut microbiome and liver cross talk. *Alcohol. Clin. Exp. Res.* 39:763.
16 Hartmann, P. 2022. Editorial: the microbiome in hepatobiliary and intestinal disease. *Front. Physiol.*13:893074.
17 Hartmann, P. and Schnabl, B. 2018. Risk factors for progression of and treatment options for NAFLD in children. *Clin. Liver Dis. (Hoboken)* 11:11. doi:10.1002/cld.685.
18 Albillos, A., Lario, M. and Alvarez-Mon, M. 2014. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. *J. Hepatol.* 61:1385. doi:10.1016/j.jhep.2014.08.010.
19 Dirchwolf, M. and Ruf, A. E. 2015. Role of systemic inflammation in cirrhosis: from pathogenesis to prognosis. *World J. Hepatol.* 7:1974.
20 D'Amico, G., Garcia-Tsao, G. and Pagliaro, L. 2006. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J. Hepatol.* 44:217. doi:10.1016/j.jhep.2005.10.013.
21 Mansour, D. and McPherson, S. 2018. Management of decompensated cirrhosis. *Clin. Med. (Lond.)* 18:s60. doi:10.7861/clinmedicine.18-2-s60.
22 European Association for the Study of the Liver. 2018. EASL clinical practice guidelines for the management of patients with decompensated cirrhosis. *J. Hepatol.* 69:406.
23 Moreau, R., Jalan, R., Gines, P. *et al.* 2013. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology* 144:1426. doi:10.1053/j.gastro.2013.02.042.
24 Arroyo, V., Moreau, R., Kamath, P. S. *et al.* 2016. Acute-on-chronic liver failure in cirrhosis. *Nat. Rev. Dis. Primers* 2:16041.
25 Clària, J., Stauber, R. E., Coenraad, M. J. *et al.* 2016. Systemic inflammation in decompensated cirrhosis: characterization and role in acute-on-chronic liver failure. *Hepatology* 64:1249.
26 Arroyo, V., García-Martinez, R. and Salvatella, X. 2014. Human serum albumin, systemic inflammation, and cirrhosis. *J. Hepatol.* 61:396. doi:10.1016/j.jhep.2014.04.012.
27 Mehta, G., Mookerjee, R. P., Sharma, V. and Jalan, R. 2015. Systemic inflammation is associated with increased intrahepatic resistance and mortality in alcohol-related acute-on-chronic liver failure. *Liver Int.* 35:724.
28 Byl, B., Roucloux, I., Crusiaux, A. *et al.* 1993. Tumor necrosis factor alpha and interleukin 6 plasma levels in

infected cirrhotic patients. *Gastroenterology* 104:1492. doi:10.1016/0016-5085(93)90361-f.
29 Bajaj, J. S., O'Leary, J. G., Reddy, K. R. *et al.* 2014. Survival in infection-related acute-on-chronic liver failure is defined by extrahepatic organ failures. . *Hepatology* 60:250.
30 Leithead, J. A., Rajoriya, N., Gunson, B. K. and Ferguson, J. W. 2015. Neutrophil-to-lymphocyte ratio predicts mortality in patients listed for liver transplantation. *Liver Int.* 35:502.
31 Lazzarotto, C., Ronsoni, M. F., Fayad, L. *et al.* 2013. Acute phase proteins for the diagnosis of bacterial infection and prediction of mortality in acute complications of cirrhosis. *Ann. Hepatol.* 12:599.
32 Khedher, S., Fouthaili, N., Maoui, A. *et al.* 2018. The diagnostic and prognostic values of C-reactive protein and procalcitonin during bacterial infections in decompensated cirrhosis. *Gastroenterol. Res. Pract.* 2018:5915947. doi:10.1155/2018/5915947.
33 Qu, J., Feng, P., Luo, Y. and Lü, X. 2016. Impact of hepatic function on serum procalcitonin for the diagnosis of bacterial infections in patients with chronic liver disease: a retrospective analysis of 324 cases. *Medicine (Baltim.)* 95:e4270. doi:10.1097/MD.0000000000004270.
34 Lin, S., Yan, Y., Wu, Y. *et al.* 2020. Procalcitonin as a biomarker for diagnose of bacterial infection in patients with acute-on-chronic liver failure. *Clin. Res. Hepatol. Gastroenterol.* 44:e32. doi:10.1016/j.clinre.2019.06.011.
35 Cervoni, J. P., Thévenot, T., Weil, D. *et al.* 2012. C-reactive protein predicts short-term mortality in patients with cirrhosis. *J. Hepatol.* 56:1299.
36 Di Martino, V., Coutris, C., Cervoni, J. P. *et al.* 2015. Prognostic value of C-reactive protein levels in patients with cirrhosis. *Liver Transpl.* 21:753.
37 Albillos, A., Martin-Mateos, R., Van der Merwe, S. *et al.* 2022. Cirrhosis-associated immune dysfunction. *Nat. Rev. Gastroenterol. Hepatol.* 19:112. doi:10.1038/s41575-021-00520-7.
38 Lehmann, J. M., Claus, K., Jansen, C. *et al.* 2018. Circulating CXCL10 in cirrhotic portal hypertension might reflect systemic inflammation and predict ACLF and mortality. *Liver Int.* 38:875.
39 Wasmuth, H. E., Kunz, D., Yagmur, E. *et al.* 2005. Patients with acute on chronic liver failure display "sepsis-like" immune paralysis. *J. Hepatol.* 42:195.
40 Queck, A., Bode, H., Uschner, F. E. *et al.* 2020. Systemic MCP-1 levels derive mainly from injured liver and are associated with complications in cirrhosis. *Front. Immunol.* 11:354.
41 Shawcross, D. L., Wright, G. A., Stadlbauer, V. *et al.* 2008. Ammonia impairs neutrophil phagocytic function in liver disease. *Hepatology* 48:1202.
42 Fiuza, C., Salcedo, M., Clemente, G. and Tellado, J. M. 2000. In vivo neutrophil dysfunction in cirrhotic patients with advanced liver disease. *J. Infect. Dis.* 182:526. doi:10.1086/315742.
43 Tritto, G., Bechlis, Z., Stadlbauer, V. *et al.* 2011. Evidence of neutrophil functional defect despite inflammation in stable cirrhosis. *J. Hepatol.* 55:574.
44 Rajkovic, I. A. and Williams, R. 1986. Abnormalities of neutrophil phagocytosis, intracellular killing and metabolic activity in alcoholic cirrhosis and hepatitis. *Hepatology* 6:252. doi:10.1002/hep.1840060217.
45 Khanam, A., Trehanpati, N., Riese, P. *et al.* 2017. Blockade of neutrophil's chemokine receptors CXCR1/2 abrogate liver damage in acute-on-chronic liver failure. *Front. Immunol.* 8:464.
46 Mookerjee, R. P., Stadlbauer, V., Lidder, S. *et al.* 2007. Neutrophil dysfunction in alcoholic hepatitis superimposed on cirrhosis is reversible and predicts the outcome. *Hepatology* 46:831.
47 Gomez, F., Ruiz, P. and Schreiber, A. D. 1994. Impaired function of macrophage Fc gamma receptors and bacterial infection in alcoholic cirrhosis. *N. Engl. J. Med.* 331:1122. doi:10.1056/NEJM199410273311704.
48 Nakagawara, A., Inokuchi, K., Ikeda, K. *et al.* 1984. Decreased superoxide (O2-)-generating activity of blood monocytes from patients with hepatic cirrhosis. *Hepatogastroenterology* 31:201.
49 Albillos, A., Hera Ad, A.eL., Reyes, E. *et al.* 2004. Tumour necrosis factor-alpha expression by activated monocytes and altered T-cell homeostasis in ascitic alcoholic cirrhosis: amelioration with norfloxacin. *J. Hepatol.* 40:624.
50 Berres, M. L., Schnyder, B., Yagmur, E. *et al.* 2009. Longitudinal monocyte human leukocyte antigen-DR expression is a prognostic marker in critically ill patients with decompensated liver cirrhosis. *Liver Int.* 29:536.
51 Berry, P. A., Antoniades, C. G., Carey, I. *et al.* 2011. Severity of the compensatory anti-inflammatory response determined by monocyte HLA-DR expression may assist outcome prediction in cirrhosis. *Intensive Care Med.* 37:453.
52 Reynolds, T. B. 2000. Ascites. *Clin. Liver Dis.* 4:151. doi:10.1016/s1089-3261(05)70101-x.
53 Ginés, P., Quintero, E., Arroyo, V. *et al.* 1987. Compensated cirrhosis: natural history and prognostic factors. *Hepatology* 7:122. doi:10.1002/hep.1840070124.
54 Kashani, A., Landaverde, C., Medici, V. and Rossaro, L. 2008. Fluid retention in cirrhosis: pathophysiology and management. *QJM* 101:71. doi:10.1093/qjmed/hcm121.
55 Planas, R., Montoliu, S., Ballesté, B. *et al.* 2006. Natural history of patients hospitalized for management of cirrhotic ascites. *Clin. Gastroenterol. Hepatol.* 4:1385.
56 Fernández, J., Navasa, M., Gómez, J. *et al.* 2002. Bacterial infections in cirrhosis: epidemiological changes with invasive procedures and norfloxacin prophylaxis. *Hepatology* 35:140. doi:10.1053/jhep.2002.30082.
57 Tariq, T., Irfan, F. B., Farishta, M. *et al.* 2019. Spontaneous fungal peritonitis: Micro-organisms, management and mortality in liver cirrhosis-A systematic review. *World J. Hepatol.* 11:596.
58 Rimola, A., García-Tsao, G., Navasa, M. *et al.* 2000. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. International Ascites Club. *J. Hepatol.* 32:142. doi:10.1016/s0168-8278(00)80201-9.
59 Simbrunner, B., Röthenbacher, A., Haslacher, H. *et al.* 2019. Ascitic fluid polymorphic nuclear cell count impacts on outcome of cirrhotic patients with ascites. *United Eur. Gastroenterol. J.* 7:651. doi:10.1177/2050640619843000.
60 Berg, R. D. and Garlington, A. W. 1979. Translocation of certain indigenous bacteria from the gastrointestinal tract to the mesenteric lymph nodes and other organs in a gnotobiotic mouse model. *Infect. Immun.* 23:403. doi:10.1128/iai.23.2.403-411.1979.
61 Wiest, R., Lawson, M. and Geuking, M. 2014. Pathological bacterial translocation in liver cirrhosis. *J. Hepatol.* 60:197. doi:10.1016/j.jhep.2013.07.044.
62 Berg, R. D. 1999. Bacterial translocation from the gastrointestinal tract. *Adv. Exp. Med. Biol.* 473:11. doi:10.1007/978-1-4615-4143-1_2.
63 Nischalke, H. D., Berger, C., Aldenhoff, K. *et al.* 2011. Toll-like receptor (TLR) 2 promoter and intron 2 polymorphisms are associated with increased risk for spontaneous bacterial peritonitis in liver cirrhosis. *J. Hepatol.* 55:1010. doi:10.1016/j.jhep.2011.02.022.
64 Bruns, T., Reuken, P. A., Fischer, J. *et al.* 2012. Further evidence for the relevance of TLR2 gene variants in spontaneous bacterial peritonitis. *J. Hepatol.* 56:1207.
65 Appenrodt, B., Grünhage, F., Gentemann, M. G. *et al.* 2010. Nucleotide-binding oligomerization domain containing 2 (NOD2) variants are genetic risk factors for death and spontaneous bacterial peritonitis in liver cirrhosis. *Hepatology* 51:1327.
66 Madrid, A. M., Hurtado, C., Venegas, M. *et al.* 2001. Long-term treatment with cisapride and antibiotics in liver cirrhosis: effect on small intestinal motility, bacterial overgrowth, and liver function. *Am. J. Gastroenterol.* 96:1251. doi:10.1111/j.1572-0241.2001.03636.x.
67 Gupta, A., Dhiman, R. K., Kumari, S. *et al.* 2010. Role of small intestinal bacterial overgrowth and delayed gastrointestinal transit time in cirrhotic patients with minimal hepatic encephalopathy. *J. Hepatol.* 53:849.
68 Brandl, K., Hartmann, P., Jih, L. J. *et al.* 2018. Dysregulation of serum bile acids and FGF19 in alcoholic hepatitis. *J. Hepatol.* 69:396.
69 Kakiyama, G., Pandak, W. M., Gillevet, P. M. *et al.* 2013. Modulation of the fecal bile acid profile by gut microbiota in cirrhosis. *J. Hepatol.* 58:949.

70 Raedsch, R., Stiehl, A., Gundert-Remy, U. *et al.* 1983. Hepatic secretion of bilirubin and biliary lipids in patients with alcoholic cirrhosis of the liver. *Digestion* 26:80. doi:10.1159/000198872.

71 Dultz, G., Piiper, A., Zeuzem, S. *et al.* 2015. Proton pump inhibitor treatment is associated with the severity of liver disease and increased mortality in patients with cirrhosis. *Aliment. Pharmacol. Ther.* 41:459. doi:10.1111/apt.13061.

72 Yang, A. M., Inamine, T., Hochrath, K. *et al.* 2017. Intestinal fungi contribute to development of alcoholic liver disease. *J. Clin. Invest.* 127:2829.

73 Hartmann, P., Lang, S., Zeng, S. *et al.* 2021. Dynamic changes of the fungal microbiome in alcohol use disorder. *Front. Physiol.* 12:699253.

74 Lang, S., Duan, Y., Liu, J. *et al.* 2020. Intestinal fungal dysbiosis and systemic immune response to fungi in patients with alcoholic hepatitis. *Hepatology* 71:522.

75 Demir, M., Lang, S., Hartmann, P. *et al.* 2022. The fecal mycobiome in non-alcoholic fatty liver disease. *J Hepatol* 76:788.

76 Bajaj, J. S., Liu, E. J., Kheradman, R. *et al.* 2018. Fungal dysbiosis in cirrhosis. *Gut* 67:1146.

77 Gravito-Soares, M., Gravito-Soares, E., Lopes, S. *et al.* 2017. Spontaneous fungal peritonitis: a rare but severe complication of liver cirrhosis. *Eur. J. Gastroenterol. Hepatol.* 29:1010. doi:10.1097/MEG.0000000000000927.

78 Bremmer, D. N., Garavaglia, J. M. and Shields, R. K. 2015. Spontaneous fungal peritonitis: a devastating complication of cirrhosis. *Mycoses* 58:387.

79 Hwang, S. Y., Yu, S. J., Lee, J. H. *et al.* 2014. Spontaneous fungal peritonitis: a severe complication in patients with advanced liver cirrhosis. *Eur. J. Clin. Microbiol. Infect. Dis.* 33:259.

80 Hartmann, P. and Schnabl, B. 2021. New developments in microbiome in alcohol-associated and nonalcoholic fatty liver disease. *Semin. Liver Dis.* 41:87. doi:10.1055/s-0040-1719174.

81 Balmer, M. L., Slack, E., de Gottardi, A. *et al.* 2014. The liver may act as a firewall mediating mutualism between the host and its gut commensal microbiota. *Sci. Transl. Med.* 6:237.

82 Assimakopoulos, S. F., Tsamandas, A. C., Tsiaoussis, G. I. *et al.* 2012. Altered intestinal tight junctions' expression in patients with liver cirrhosis: a pathogenetic mechanism of intestinal hyperpermeability. *Eur. J. Clin. Invest.* 42:439.

83 Pijls, K. E., Koek, G. H., Elamin, E. E. *et al.* 2014. Large intestine permeability is increased in patients with compensated liver cirrhosis. *Am. J. Physiol. Gastrointest. Liver Physiol.* 306:G147.

84 Du Plessis, J., Vanheel, H., Janssen, C. E. *et al.* 2013. Activated intestinal macrophages in patients with cirrhosis release NO and IL-6 that may disrupt intestinal barrier function. *J. Hepatol.* 58:1125.

85 Munoz, L., Jose Borrero, M., Ubeda, M. *et al.* 2012. Interaction between intestinal dendritic cells and bacteria translocated from the gut in rats with cirrhosis. *Hepatology* 56:1861. doi:10.1002/hep.25854.

86 Muñoz, L., Albillos, A., Nieto, M. *et al.* 2005. Mesenteric Th1 polarization and monocyte TNF-alpha production: first steps to systemic inflammation in rats with cirrhosis. *Hepatology* 42:411. doi:10.1002/hep.20799.

87 Úbeda, M., Muñoz, L., Borrero, M. J. *et al.* 2010. Critical role of the liver in the induction of systemic inflammation in rats with preascitic cirrhosis. *Hepatology* 52:2086.

88 Hartmann, P., Haimerl, M., Mazagova, M. *et al.* 2012. Toll-like receptor 2-mediated intestinal injury and enteric tumor necrosis factor receptor I contribute to liver fibrosis in mice. *Gastroenterology* 143:1330.

89 Jenne, C. N. and Kubes, P. 2013. Immune surveillance by the liver. *Nat. Immunol.* 14:996.

90 Su, G. L., Klein, R. D., Aminlari, A. *et al.* 2000. Kupffer cell activation by lipopolysaccharide in rats: role for lipopolysaccharide binding protein and toll-like receptor 4. *Hepatology* 31:932. doi:10.1053/he.2000.5634.

91 Schumann, R. R., Kirschning, C. J., Unbehaun, A. *et al.* 1996. The lipopolysaccharide-binding protein is a secretory class 1 acute-phase protein whose gene is transcriptionally activated by APRF/STAT/3 and other cytokine-inducible nuclear proteins. *Mol. Cell. Biol.* 16:3490. doi:10.1128/MCB.16.7.3490.

92 Fox, E. S., Thomas, P. and Broitman, S. A. 1989. Clearance of gut-derived endotoxins by the liver. Release and modification of 3H, 14C-lipopolysaccharide by isolated rat Kupffer cells. *Gastroenterology* 96:456. doi:10.1016/0016-5085(89)91571-0.

93 Duan, Y., Chu, H., Brandl, K. *et al.* 2021. CRIg on liver macrophages clears pathobionts and protects against alcoholic liver disease. *Nat. Commun.* 12:7172.

94 Helmy, K. Y., Katschke, K. J., Gorgani, N. N. *et al.* 2006. CRIg: a macrophage complement receptor required for phagocytosis of circulating pathogens. *Cell* 124:915.

95 Wiesmann, C., Katschke, K. J., Yin, J. *et al.* 2006. Structure of C3b in complex with CRIg gives insights into regulation of complement activation. *Nature* 444:217.

96 Zeng, Z., Surewaard, B. G., Wong, C. H. *et al.* 2016. CRIg functions as a macrophage pattern recognition receptor to directly bind and capture blood-borne Gram-positive bacteria. *Cell Host Microbe* 20:99.

97 Reißing, J., Lutz, P., Frissen, M. *et al.* 2022. Immunomodulatory receptor VSIG4 is released during spontaneous bacterial peritonitis and predicts short-term mortality. *JHEP Rep.* 4:100391.

98 Rimola, A., Soto, R., Bory, F. *et al.* 1984. Reticuloendothelial system phagocytic activity in cirrhosis and its relation to bacterial infections and prognosis. *Hepatology* 4:53. doi:10.1002/hep.1840040109.

99 Runyon, B. A., Morrissey, R. L., Hoefs, J. C. and Wyle, F. A. 1985. Opsonic activity of human ascitic fluid: a potentially important protective mechanism against spontaneous bacterial peritonitis. *Hepatology* 5:634. doi:10.1002/hep.1840050419.

100 Runyon, B. A. 1988. Patients with deficient ascitic fluid opsonic activity are predisposed to spontaneous bacterial peritonitis. *Hepatology* 8:632. doi:10.1002/hep.1840080332.

101 Mustafa, G., Khan, M., Alam, K. *et al.* 2007. Study on ascitic fluid complement 3 level in cirrhotic patients with spontaneous bacterial peritonitis and without spontaneous bacterial peritonitis. *Hepatogastroenterology* 54:1905.

102 Chen, S. M., Lo, G. H., Lai, K. H. *et al.* 1994. Serum and ascitic concentration of C3, C4 and protein in cirrhotic patients with spontaneous bacterial peritonitis. *Zhonghua Yi Xue Za Zhi (Taipei)* 54:87.

103 Homann, C., Varming, K., Høgåsen, K. *et al.* 1997. Acquired C3 deficiency in patients with alcoholic cirrhosis predisposes to infection and increased mortality. *Gut* 40:544. doi:10.1136/gut.40.4.544.

104 Ono, Y., Watanabe, T., Matsumoto, K. *et al.* 2004. Opsonophagocytic dysfunction in patients with liver cirrhosis and low responses to tumor necrosis factor-alpha and lipopolysaccharide in patients' blood. *J. Infect. Chemother.* 10:200. doi:10.1007/s10156-004-0321-7.

105 Akalin, H. E., Laleli, Y. and Telatar, H. 1983. Bactericidal and opsonic activity of ascitic fluid from cirrhotic and non-cirrhotic patients. *J. Infect. Dis.* 147:1011. doi:10.1093/infdis/147.6.1011.

106 Shen, H., French, B. A., Liu, H. *et al.* 2014. Increased activity of the complement system in the liver of patients with alcoholic hepatitis. *Exp. Mol. Pathol.* 97:338.

107 Bouwman, L. H., Roos, A., Terpstra, O. T. *et al.* 2005. Mannose binding lectin gene polymorphisms confer a major risk for severe infections after liver transplantation. *Gastroenterology* 129:408.

108 Altorjay, I., Vitalis, Z., Tornai, I. *et al.* 2010. Mannose-binding lectin deficiency confers risk for bacterial infections in a large Hungarian cohort of patients with liver cirrhosis. *J. Hepatol.* 53:484.

109 Lombardo-Quezada, J., Sanclemente, G., Colmenero, J. *et al.* 2018. Mannose-binding lectin-deficient donors increase the risk of bacterial infection and bacterial infection-related mortality after liver transplantation. *Am. J. Transplant.* 18:197. doi:10.1111/ajt.14408.

110 Worthley, D. L., Johnson, D. F., Eisen, D. P. *et al.* 2009. Donor mannose-binding lectin deficiency increases the likelihood of clinically significant infection after liver transplantation. *Clin. Infect. Dis.* 48:410.

111 de Rooij, B. J., van Hoek, B., ten Hove, W. R. *et al.* 2010. Lectin complement pathway gene profile of donor and recipient determine the risk of bacterial infections after orthotopic liver transplantation. *Hepatology* 52:1100.

112 Qamar, A. A. and Grace, N. D. 2009. Abnormal hematological indices in cirrhosis. *Can. J. Gastroenterol.* 23:441. doi:10.1155/2009/591317.

113 Bukong, T. N., Cho, Y., Iracheta-Vellve, A. *et al.* 2018. Abnormal neutrophil traps and impaired efferocytosis contribute to liver injury and sepsis severity after binge alcohol use. *J. Hepatol.* 69:1145.

114 Dale, D. C., Boxer, L. and Liles, W. C. 2008. The phagocytes: neutrophils and monocytes. *Blood* 112:935.

115 Ambruso, D. R., Knall, C., Abell, A. N. *et al.* 2000. Human neutrophil immunodeficiency syndrome is associated with an inhibitory Rac2 mutation. *Proc. Natl. Acad. Sci. USA.* 97:4654. doi:10.1073/pnas.080074897.

116 Zimmermann, H. W., Seidler, S., Nattermann, J. *et al.* 2010. Functional contribution of elevated circulating and hepatic nonclassical CD14CD16 monocytes to inflammation and human liver fibrosis. *PLoS One* 5:e11049.

117 Seidler, S., Zimmermann, H. W., Weiskirchen, R. *et al.* 2012. Elevated circulating soluble interleukin-2 receptor in patients with chronic liver diseases is associated with non-classical monocytes. *BMC Gastroenterol.* 12:38.

118 Hassner, A., Kletter, Y., Jedvab, M. *et al.* 1979. Impaired monocyte function in liver cirrhosis. *Lancet* 1:329. doi:10.1016/s0140-6736(79)90745-1.

119 Hassner, A., Kletter, Y., Shlag, D. *et al.* 1981. Impaired monocyte function in liver cirrhosis. *Br. Med. J. (Clin. Res. Ed.)* 282:1262. doi:10.1136/bmj.282.6272.1262.

120 Holdstock, G., Leslie, B., Hill, S. *et al.* 1982. Monocyte function in cirrhosis. *J. Clin. Pathol.* 35:972. doi:10.1136/jcp.35.9.972.

121 Mørland, B. and Mørland, J. 1987. Effects of ethanol on human monocyte IgG Fc receptors. *Scand. J. Immunol.* 26:187. doi:10.1111/j.1365-3083.1987.tb02250.x.

122 Zhang, J. Y., Zou, Z. S., Huang, A. *et al.* 2011. Hyper-activated pro-inflammatory CD16 monocytes correlate with the severity of liver injury and fibrosis in patients with chronic hepatitis B. *PLoS One* 6:e17484.

123 Gäbele, E., Mühlbauer, M., Paulo, H. *et al.* 2009. Analysis of monocyte chemotactic protein-1 gene polymorphism in patients with spontaneous bacterial peritonitis. *World J. Gastroenterol.* 15:5558. doi:10.3748/wjg.15.5558.

124 Laso, F. J., Almeida, J., Torres, E. *et al.* 2010. Chronic alcohol consumption is associated with an increased cytotoxic profile of circulating lymphocytes that may be related with the development of liver injury. *Alcohol. Clin. Exp. Res.* 34:876.

125 Laso, F. J., Madruga, J. I., Girón, J. A. *et al.* 1997. Decreased natural killer cytotoxic activity in chronic alcoholism is associated with alcohol liver disease but not active ethanol consumption. *Hepatology* 25:1096. doi:10.1002/hep.510250508.

126 Chuang, W. L., Liu, H. W., Chang, W. Y. *et al.* 1991. Natural killer cell activity in patients with liver cirrhosis relative to severity of liver damage. *Dig. Dis. Sci.* 36:299. doi:10.1007/BF01318200.

127 Ben-Eliyahu, S., Page, G. G., Yirmiya, R. and Taylor, A. N. 1996. Acute alcohol intoxication suppresses natural killer cell activity and promotes tumor metastasis. *Nat. Med.* 2:457. doi:10.1038/nm0496-457.

128 Nakachi, K. and Imai, K. 1992. Environmental and physiological influences on human natural killer cell activity in relation to good health practices. *Jpn. J. Cancer Res.* 83:798. doi:10.1111/j.1349-7006.1992.tb01983.x.

129 Glässner, A., Eisenhardt, M., Krämer, B. *et al.* 2012. NK cells from HCV-infected patients effectively induce apoptosis of activated primary human hepatic stellate cells in a TRAIL-, FasL- and NKG2D-dependent manner. *Lab. Invest.* 92:967. doi:10.1038/labinvest.2012.54.

130 Krämer, B., Körner, C., Kebschull, M. *et al.* 2012. Natural killer p46High expression defines a natural killer cell subset that is potentially involved in control of hepatitis C virus replication and modulation of liver fibrosis. *Hepatology* 56:1201.

131 Gur, C., Doron, S., Kfir-Erenfeld, S. *et al.* 2012. NKp46-mediated killing of human and mouse hepatic stellate cells attenuates liver fibrosis. *Gut* 61:885. doi:10.1136/gutjnl-2011-301400.

132 Espinoza, J. L., Nguyen, V. H., Ichimura, H. *et al.* 2016. A functional polymorphism in the NKG2D gene modulates NK-cell cytotoxicity and is associated with susceptibility to Human Papilloma Virus-related cancers. *Sci. Rep.* 6:39231.

133 Narni-Mancinelli, E., Jaeger, B. N., Bernat, C. *et al.* 2012. Tuning of natural killer cell reactivity by NKp46 and Helios calibrates T cell responses. *Science* 335:344.

134 Cook, R. T., Waldschmidt, T. J., Cook, B. L. *et al.* 1996. Loss of the CD5+ and CD45RAhi B cell subsets in alcoholics. *Clin. Exp. Immunol.* 103:304. doi:10.1046/j.1365-2249.1996.d01-621.x.

135 Laso, F. J., Madruga, J. I., López, A. *et al.* 1996. Distribution of peripheral blood lymphoid subsets in alcoholic liver cirrhosis: influence of ethanol intake. *Alcohol. Clin. Exp. Res.* 20:1564. doi:10.1111/j.1530-0277.1996.tb01700.x.

136 Massonnet, B., Delwail, A., Ayrault, J. M. *et al.* 2009. Increased immunoglobulin A in alcoholic liver cirrhosis: exploring the response of B cells to Toll-like receptor 9 activation. *Clin. Exp. Immunol.* 158:115.

137 Doi, H., Iyer, T. K., Carpenter, E. *et al.* 2012. Dysfunctional B-cell activation in cirrhosis resulting from hepatitis C infection associated with disappearance of CD27-positive B-cell population. *Hepatology* 55:709.

138 Sacanella, E., Estruch, R., Gayà, A. *et al.* 1998. Activated lymphocytes (CD25+ CD69+ cells) and decreased CD19+ cells in well-nourished chronic alcoholics without ethanol-related diseases. *Alcohol. Clin. Exp. Res.* 22:897. doi:10.1111/j.1530-0277.1998.tb03886.x.

139 Mili, F., Flanders, W. D., Boring, J. R. *et al.* 1992. The associations of alcohol drinking and drinking cessation to measures of the immune system in middle-aged men. *Alcohol. Clin. Exp. Res.* 16:688. doi:10.1111/j.1530-0277.1992.tb00662.x.

140 Pasala, S., Barr, T. and Messaoudi, I. 2015. Impact of alcohol abuse on the adaptive immune system. *Alcohol Res.* 37:185.

141 Smith, W. I., Van Thiel, D. H., Whiteside, T. *et al.* 1980. Altered immunity in male patients with alcoholic liver disease: evidence for defective immune regulation. *Alcohol. Clin. Exp. Res.* 4:199. doi:10.1111/j.1530-0277.1980.tb05635.x.

142 Tsukada, S., Saffran, D. C., Rawlings, D. J. *et al.* 1993. Deficient expression of a B cell cytoplasmic tyrosine kinase in human X-linked agammaglobulinemia. *Cell* 72:279. doi:10.1016/0092-8674(93)90667-f.

143 Perrin, D., Bignon, J. D., Beaujard, E. and Cheneau, M. L. 1984. Populations of circulating T lymphocytes in patients with alcoholic cirrhosis. *Gastroenterol. Clin. Biol.* 8:907.

144 Morita, K., Fukuda, Y., Nakano, I. *et al.* 2005. Peripheral lymphocyte subsets vary with stage of hepatitis C virus-associated liver disease. *Hepatogastroenterology* 52:1803.

145 McGovern, B. H., Golan, Y., Lopez, M. *et al.* 2007. The impact of cirrhosis on CD4+ T cell counts in HIV-seronegative patients. *Clin. Infect. Dis.* 44:431.

146 Márquez, M., Fernández-Gutiérrez, C., Montes-de-Oca, M. *et al.* 2009. Chronic antigenic stimuli as a possible explanation for the immunodepression caused by liver cirrhosis. *Clin. Exp. Immunol.* 158:219.

147 Devière, J., Denys, C., Schandene, L. *et al.* 1988. Decreased proliferative activity associated with activation markers in patients with alcoholic liver cirrhosis. *Clin. Exp. Immunol.* 72:377.

148 Morishima, C., Di Bisceglie, A. M., Rothman, A. L. *et al.* 2012. Antigen-specific T lymphocyte proliferation decreases over time in advanced chronic hepatitis C. *J. Viral Hepatol.* 19:404.

149 Bray, L. A., Shao, H. and Ewald, S. J. 1993. Effect of ethanol on development of fetal mouse thymocytes in organ culture. *Cell. Immunol.* 151:12.

150 Saad, A. J. and Jerrells, T. R. 1991. Flow cytometric and immunohistochemical evaluation of ethanol-induced changes in splenic and thymic lymphoid cell populations. *Alcohol. Clin. Exp. Res.* 15:796.

151 Kapasi, A. A., Patel, G., Goenka, A. *et al.* 2003. Ethanol promotes T cell apoptosis through the mitochondrial pathway. *Immunology* 108:313.

152 Santiago, J. L., Sánchez-Pérez, L., Pérez-Flores, I. *et al.* 2021. Association of polymorphisms in T-cell activation costimulatory/inhibitory signal genes with allograft kidney rejection risk. *Front. Immunol.* 12:650979.

153 Mörbe, U. M., Jørgensen, P. B., Fenton, T. M. *et al.* 2021. Human gut-associated lymphoid tissues (GALT); diversity, structure, and function. *Mucosal Immunol.* 14:793.

154 Sibley, D. and Jerrells, T. R. 2000. Alcohol consumption by C57BL/6 mice is associated with depletion of lymphoid cells from the gut-associated lymphoid tissues and altered resistance to oral infections with *Salmonella typhimurium*. *J. Infect. Dis.* 182:482.

155 Sibley, D. A., Fuseler, J., Slukvin, I. and Jerrells, T. R. 1995. Ethanol-induced depletion of lymphocytes from the mesenteric lymph nodes of C57B1/6 mice is associated with RNA but not DNA degradation. *Alcohol. Clin. Exp. Res.* 19:324.

156 Souza, H. S., Elia, C. C., Braulio, V. B. *et al.* 2003. Effects of ethanol on gut-associated lymphoid tissues in a model of bacterial translocation: a possible role of apoptosis. *Alcohol* 30:183.

157 Yan, A. W., Fouts, D. E., Brandl, J. *et al.* 2011. Enteric dysbiosis associated with a mouse model of alcoholic liver disease. *Hepatology* 53:96.

158 Hartmann, P., Chen, P., Wang, H. J. *et al.* 2013. Deficiency of intestinal mucin-2 ameliorates experimental alcoholic liver disease in mice. *Hepatology* 58:108.

159 Teltschik, Z., Wiest, R., Beisner, J. *et al.* 2012. Intestinal bacterial translocation in rats with cirrhosis is related to compromised Paneth cell antimicrobial host defense. *Hepatology* 55:1154.

160 Sargenti, K., Prytz, H., Nilsson, E. and Kalaitzakis, E. 2015. Predictors of mortality among patients with compensated and decompensated liver cirrhosis: the role of bacterial infections and infection-related acute-on-chronic liver failure. *Scand. J. Gastroenterol.* 50:875.

161 Grangé, J. D., Roulot, D., Pelletier, G. *et al.* 1998. Norfloxacin primary prophylaxis of bacterial infections in cirrhotic patients with ascites: a double-blind randomized trial. *J. Hepatol.* 29:430.

162 Moreau, R., Elkrief, L., Bureau, C. *et al.* 2018. Effects of long-term norfloxacin therapy in patients with advanced cirrhosis. *Gastroenterology* 155:1816.

163 Ginés, P., Rimola, A., Planas, R. *et al.* 1990. Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis: results of a double-blind, placebo-controlled trial. *Hepatology* 12:716.

164 Fernández, J., Acevedo, J., Castro, M. *et al.* 2012. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: a prospective study. *Hepatology* 55:1551.

165 Fernández, J., Prado, V., Trebicka, J. *et al.* 2019. Multidrug-resistant bacterial infections in patients with decompensated cirrhosis and with acute-on-chronic liver failure in Europe. *J. Hepatol.* 70:398.

166 Philips, C. A., Phadke, N., Ganesan, K. *et al.* 2018. Corticosteroids, nutrition, pentoxifylline, or fecal microbiota transplantation for severe alcoholic hepatitis. *Indian J. Gastroenterol.* 37:215.

167 Philips, C. A., Ahamed, R., Rajesh, S. *et al.* 2022. Long-term outcomes of stool transplant in alcohol-associated hepatitis --analysis of clinical outcomes, relapse, gut microbiota and comparisons with standard care. *J. Clin. Exp. Hepatol.* 12:1124.

168 O'Brien, A. J., Fullerton, J. N., Massey, K. A. *et al.* 2014. Immunosuppression in acutely decompensated cirrhosis is mediated by prostaglandin E2. *Nat. Med.* 20:518.

169 Henriksen, J. H., Ring-Larsen, H. and Christensen, N. J. 1987. Hepatic intestinal uptake and release of catecholamines in alcoholic cirrhosis. Evidence of enhanced hepatic intestinal sympathetic nervous activity. *Gut* 28:1637.

170 Sort, P., Navasa, M., Arroyo, V. *et al.* 1999. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N. Engl. J. Med.* 341:403.

171 Caraceni, P., Riggio, O., Angeli, P. *et al.* 2018. Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomised trial. *Lancet* 391:2417.

172 Lee, K. C., Baker, L. A., Stanzani, G. *et al.* 2015. Extracorporeal liver assist device to exchange albumin and remove endotoxin in acute liver failure: results of a pivotal pre-clinical study. *J. Hepatol.* 63:634.

173 Chang, H. K., Chang, E. Y., Ryu, S. and Han, S. J. 2016. Cyclooxygenase-2 inhibitor reduces hepatic stiffness in pediatric chronic liver disease patients following Kasai portoenterostomy. *Yonsei Med. J.* 57:893.

174 Mookerjee, R. P., Pavesi, M., Thomsen, K. L. *et al.* 2016. Treatment with non-selective beta blockers is associated with reduced severity of systemic inflammation and improved survival of patients with acute-on-chronic liver failure. *J. Hepatol.* 64:574.

175 Kumar, M., Kainth, S., Choudhury, A. *et al.* 2019. Treatment with carvedilol improves survival of patients with acute-on-chronic liver failure: a randomized controlled trial. *Hepatol. Int.* 13:800.

176 Bihari, C., Anand, L., Rooge, S. *et al.* 2016. Bone marrow stem cells and their niche components are adversely affected in advanced cirrhosis of the liver. *Hepatology* 64:1273.

177 Verma, N., Kaur, A., Sharma, R. *et al.* 2018. Outcomes after multiple courses of granulocyte colony-stimulating factor and growth hormone in decompensated cirrhosis: a randomized trial. *Hepatology* 68:1559.

178 Garg, V., Garg, H., Khan, A. *et al.* 2012. Granulocyte colony-stimulating factor mobilizes CD34(+) cells and improves survival of patients with acute-on-chronic liver failure. *Gastroenterology* 142:505.

179 Engelmann, C., Herber, A., Franke, A. *et al.* 2021. Granulocyte-colony stimulating factor (G-CSF) to treat acute-on-chronic liver failure: a multicenter randomized trial (GRAFT study). *J. Hepatol.* 75:1346.

180 Shi, M., Zhang, Z., Xu, R. *et al.* 2012. Human mesenchymal stem cell transfusion is safe and improves liver function in acute-on-chronic liver failure patients. *Stem Cells Transl. Med.* 1:725.

181 Lin, B. L., Chen, J. F., Qiu, W. H. *et al.* 2017. Allogeneic bone marrow-derived mesenchymal stromal cells for hepatitis B virus-related acute-on-chronic liver failure: a randomized controlled trial. *Hepatology* 66:209.

182 Nevens, F., Gustot, T., Laterre, P. F. *et al.* 2021. A phase II study of human allogeneic liver-derived progenitor cell therapy for acute-on-chronic liver failure and acute decompensation. *JHEP Rep.* 3:100291.

183 Najimi, M., Berardis, S., El-Kehdy, H. *et al.* 2017. Human liver mesenchymal stem/progenitor cells inhibit hepatic stellate cell activation: in vitro and in vivo evaluation. *Stem Cell Res. Ther.* 8:131.